3,4-Dihydroxyphenylalanine (DOPA) Decarboxylase Deficiency and Resultant High Levels of Plasma DOPA and Dopamine in Unfavorable Neuroblastoma

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Neuroblastoma (NB) is a tumor which arises from neural crest cells. In the developing neural crest cells, the induction of 3,4-dihydroxyphenylalanine (DOPA) decarboxylase is more delayed than that of tyrosine hydroxylase and dopamine-β-hydroxylase. If NB cells are arrested in an early stage of neural crest development, the induction of DOPA decarboxylase is insufficient and the accumulation and secretion of DOPA can be caused. The biochemically immature phenotype is thought to represent the undifferentiated characteristics of the cells and might correlate with the grade of malignancy. To investigate whether the hypothesis is clinically applicable or not, we have measured plasma DOPA, dopamine and urinary catecholamine metabolites in NB patients. The levels of plasma DOPA, dopamine, urinary homovanillic acid (HVA) and vanillactic acid (VLA) were significantly higher in patients with unfavorable NBs and the higher plasma DOPA level was significantly associated with the patients' age (> 1 year old), tumor stage (III, IV) and DNA diploidy. Serial determination of plasma DOPA was a good monitor of the disease course. These results are compatible with the hypothesis on DOPA decarboxylase deficiency and DOPA secretion in undifferentiated, unfavorable NBs. In conclusion, the plasma DOPA can be used to predict patients' prognosis as well as to follow up patients with NB. (Hypertens Res 1995; 18 Suppl. 1: S209-S210)

Key Words: neuroblastoma, 3,4-dihydroxyphenylalanine (DOPA), DOPA decarboxylase

Neuroblastoma is a childhood malignant tumor which arises from neural crest cells and produces catecholamines and their metabolites. Our previous studies on the catecholamine metabolism in neuroblastoma cell lines showed that some neuroblastoma cells lacked 3,4-dihydroxyphenylalanine (DOPA) decarboxylase activity relative to that of tyrosine hydroxylase and, as a result, DOPA accumulated in these cells (1, 2). On the other hand, the activity of DOPA decarboxylase is higher than that of tyrosine hydroxylase in the normal catecholaminergic cells of sympathetic tissue or the adrenal gland. Tyrosine hydroxylase is the rate limiting enzyme in catecholamine synthesis and this is the reason why DOPA does not accumulate and is hardly detected in normal cells. Teitelman et al. showed that the induction of DOPA decarboxylase was more delayed than that of tyrosine hydroxylase and dopamine-β-hydroxylase in the developing neural crest cells (3). Based on this observation, it is hypothesized that neuroblastoma cells are arrested in an early stage of neural crest development, in which the insufficient induction of DOPA decarboxylase causes accumulation and secretion of DOPA (Fig. 1). If this is the case, DOPA decarboxylase deficiency could be associated with the undifferentiated characteristics of the cells and might be correlated with the grade of malignancy of the tumor. In this paper, we report the results which were obtained from neuroblastoma patients when investigating the clinical applicability of the hypothesis.

Catecholamine Metabolism in Neuroblastoma

We measured catecholamine metabolites including plasma DOPA and dopamine in neuroblastoma patients. Abnormally high levels of plasma DOPA were demonstrated in patients with neuroblastoma and the levels in patients with other solid tumors were all within the normal range (< 9,400 pg/ml) (4). The levels of plasma DOPA in patients with clinical manifestations (mean, 76,500 pg/ml; range, 17,700-220,000 pg/ml) were significantly higher than those in patients detected by screening (mean, 8,283 pg/ml; range 2,890-33,300 pg/ml, p < 0.01). The levels of plasma dopamine, urinary homovanillic acid (HVA) and vanillactic acid (VLA) were also significantly higher in patients with clinical manifestations (4). The catecholamine secretion profile in neuroblastoma was interpreted as follows. While the catecholamine pathway is biochemically maturer and DOPA is not secreted in favorable, screening-detected neuroblastomas, the cells are less...
differentiated and the catecholamine pathway is immature in unfavorable, clinically-diagnosed neuroblastomas. The relative deficiency of DOPA decarboxylase causes an overflow of DOPA, which is metabolized to VLA and HVA, in the latter tumors (Fig. 2). We think that a part of plasma DOPA is converted to dopamine by plasma DOPA decarboxylase activity which is often detected in patients’ plasma (3) and results in the higher levels of plasma dopamine in patients with unfavorable neuroblastoma.

**Plasma DOPA as a Tumor Marker of Neuroblastoma**

The plasma levels of DOPA and dopamine were significantly higher in patients with clinical manifestations whose prognosis was apparently poorer than those with screening-detected tumors. Particularly, the higher plasma DOPA levels were significantly correlated with the patients’ age (>1 year old), advanced stages (III, IV) and DNA diploidy, all of which were associated with the unfavorable characteristics of neuroblastoma (4). These results indicate that plasma DOPA is available in predicting patients’ prognosis as well as in making a diagnosis of neuroblastoma. In addition, plasma DOPA levels responded to the treatment and serial determination was a good monitor of the disease course, which indicates that plasma DOPA is a useful marker in the follow-up of neuroblastoma as well.

**Conclusion**

Our study showed that the levels of plasma DOPA and dopamine are high in patients with unfavorable neuroblastoma and that the plasma DOPA level is available in predicting patients’ prognosis. The hypothesis as to the expression of catecholamine phenotype in neuroblastoma, which is based on the developmental biology of the neural crest cells, seems to be supported.

**References**